Why are East Asians more susceptible to several infection-associated cancers (carcinomas of the nasopharynx, stomach, liver, adenocarcinoma of the lung, nasal NK/T-cell lymphomas)?

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ABSTRACT

There are at least five cancers with uniquely high incidence amongst East and Southeast Asian ethnic groups – namely nasopharyngeal carcinoma (NPC); gastric carcinoma; hepatocellular carcinoma (HCC); adeno-carcinoma of the lung in female non-smokers and nasal NK/T-cell lymphomas. They all appear to be related to an infective cause (Epstein Barr Virus, Helicobacter pylori, hepatitis B virus). We hypothesize that a genetic bottleneck 30,000 years ago at the Last Glacial Maximum could have resulted in unique genetic polymorphisms in Toll-like receptor 8, making East Asians more vulnerable to these infective associated cancers. This bottleneck could have been caused by the presence of malaria in the southern Himalayan conduit between central and East Asia; and only those with an attenuated innate immune response to the malarial parasite (perhaps reflected by the TLR8 polymorphism) were spared the ravages of cerebral malaria; allowing these people to cross into east Asia, but then rendering them susceptible to later endemic infections and their associated cancers.

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Introduction

There are at least five cancers with uniquely high incidence amongst East and Southeast Asian ethnic groups – namely nasopharyngeal cancer (NPC); gastric cancer; hepatocellular carcinoma (HCC); adeno-carcinoma of the lung in female non-smokers and nasal NK/T-cell lymphomas.

We will attempt to describe certain unique characteristics of each of these cancers and come to a unifying hypothesis why these cancers should have such distinctive epidemiological characteristics.

Background

Nasopharyngeal cancer

Wee et al. [1] first postulated from the migration histories of the peoples of Southeast Asia that there was potentially a disease susceptibility gene for NPC, which appeared to have been derived from a reference population – the Bai-Yue. This ancestral population can be marked by the Y chromosome Haplogroup O-1A – M119 marker that is the precursors of today’s Tai-Kedai speaking populations in the Southeast Asian Massif. The Austronesian speaking peoples who are believed to have been derived from this population [2] then carried the disease susceptibility to to Islandic Southeast Asia, and to as far west as Madagascar and as far east as the Easter Islands [3]. Today all populations at risk of NPC in this part of the world can trace some blood linkage to either of these two populations (Fig. 1).

Wee also noted that there appeared to be a step-wise “dilution” of NPC incidence with each successive migration and intermarriage of a higher risk ethnic minority population to a lower risk indigenous majority population. For example, the reference Bai-Yue population comprises the isolated aboriginal populations of Borneo (Bidayuh) and Hainan island and the Tanka boat people (who were genetic isolates by imperial decree). A recent phylogenetic analysis of mtDNA lineages indicate that the ancestral types of lineages found in the Bidayuh of Borneo tend to be found in Indochina or South China. This is characterized by haplogroups M21a, N9a6, N21, N22 and F1a which account for more than 60% of their mtDNA lineages. The timing of this “migration” may have ranged from 30,000 to 10,000 YBP based on the age estimates of mtDNA haplogroups [4].

The Cantonese, being derived from low risk northern Han marrying high risk Southern Natives then have an incidence of NPC...
that is halved that of the original Bai-Yue population. Similarly
when the minority Bai-Yue (or Tai) or minority Austronesian pop-
ulation married with the majority Austro-Asiatic indigenous pop-
ulations of both mainland (e.g. Thai, Lao, South Vietnamese) and
islandic Southeast Asia (Malays, Filipino, Indonesians) – the resul-
tant population incidence of NPC again halved. Then when the
Austronesians moved further East (Polynesians) or West (Mada-
gascans); the NPC incidences in these resultant populations again
halved.

Wee went onto hypothesize that there appeared to be a female
transmission, as evidenced by the fact that the Cantonese (a rela-
tively high risk for NPC ethnic group) had a paternal ancestry from
the Northern Hans (a low risk for NPC ethnic group) and a maternal
ancestry which was predominantly from the Southern Natives
(high risk for NPC ethnic group) [5]; the mtDNA of the “at risk
for NPC” populations all appeared to have a more consistent South-
east Asian signature compared with the more varied Y chromo-
some signatures [3,5,6]; The ancient Austronesian societies also
tended to be matrilocal [7].

A suggestion of female transmission would then leave the
X-chromosome or mtDNA as possible candidates for the site of
the NPC disease susceptibility gene. Day et al. [8,9], has on several
occasions postulated a recessive NPC gene closely linked to the
HLA region as a major determinant of the Chinese risk for the dis-
ease. However, that NPC has a consistent 3:1 male to female pre-
ponderance, and the fact that Cantonese have paternal ancestry
with low risk of NPC (Northern Han) and a maternal ancestry with
high risk of NPC (Southern native) could also argue for a probable
x-linked recessive inheritance.

Hence Wee went onto postulate a 2-hit hypothesis [10] that
could account for the stark population differences in the risks for
developing NPC as well as the known association between the
HLA genes and NPC. He hypothesized that these hits probably
occur during the EBV infection phase of the whole carcinogenic
process, and involves the immune system.

Wee suggests that the 1st hit (involving an x-linked recessive
SNP affecting the innate immune response) – would probably al-
low the EBV virus to infect and enter the post-nasal epithelial mu-
cosa, and is probably an “innocuous” event with no carcinogenic
consequences without the next hit. The 2nd hit then involves the
body’s inability to mount an HLA based effective immune response
which would now result in proliferation of EBV in the infected
cells, and continuation with the carcinogenic cascade and finally
resulting in NPC. Such a hypothesis may well then explain why
only certain populations appear to be at risk (i.e. there must be
Austronesian/Tai-Kedai blood ties) and why certain HLA groups
are protective while other HLA groups are associated with NPC.
Current GWAS studies, which unfortunately specifically exclude
the X-chromosome in their analyses, all consistently support the
role of the HLA genes, but does not adequately explain the popula-
tion differences [11–13].

Various authors [14,15], have consistently suggested that EBV
infection is an early initiating event in NPC carcinogenesis; and
one of the major questions surrounding NPC is how the EBV-in-
fected cell can escape the immune response. The 2-hit hypothesis,
whereby with the 2nd hit, the appropriate T cells is supposed to re-
move the EBV infection, would help to explain this observation. In
a patient with a “susceptible” HLA phenotype, it is possible that the
T cell response is not fully competent, resulting in the EB virus
escaping the cell mediated immune response and thus allowing
the carcinogenic process to proceed. Recent studies in Hodgkin’s
lymphoma (HL) [16] which in some is also EBV related, suggest
that HLA related T cell responses and events in the early immune
response to EBV infection in infectious mononucleosis (IMS) play
critical roles in the pathogenesis of EBV-related HL.

The 1st-hit involving the innate immune response would then
give rise to a list of probable genes on the X-chromosome includ-
ing Toll-like receptors (TLR) 7 and 8; the IRAK gene and the NEMO
gen. TLR-8 (Xp22) stands as a possible prime candidate as polymorphisms in this gene in Chinese and Japanese are uniquely